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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,187	03/18/2004	Thomas Christoph	029310.53299US	5120

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EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,187	CHRISTOPH, THOMAS	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-41,48,50,51,54-57 and 73* is/are pending in the application.

4a) Of the above claim(s) *38,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,48,50,51,54-57 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/10 has been entered.

Status of Claims

1. Claims 37-41, 48, 50, 51, 54-57, and 73 are pending in this application.

2. Cancellation of claims 49, 52, and 53 is acknowledged. Claims 1-36, 42-47, and 58-72 already stand canceled.

3. Claims 38, 40, and 41 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 9/27/07.

4. Claims 37, 39, 48, 50, 51, 54-57, and 73 are examined.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 37, 39, 48, 50, 51, 54-57, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595 and cited by Applicant), in view of Buschmann (US Patent 6248,737) and Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947 and cited by Applicant).

The claimed invention is drawn to a composition comprising an admixture of an analgesic and oxybutynin (see claim 37); Applicants have elected (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride as the analgesic (see claims 37, 39, 48, 50, 51, and 54-57).

Chutka et al teach that both anticholinergic drugs (i.e., antimuscarinic agents) and opioids can decrease the contraction of the detrusor by impairing the contractility of the detrusor and potentially lead to urinary retention (see, e.g., page 593, third paragraph, and Table 1).

Chutka et al do not specifically teach the combination of an analgesic such as (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent such as oxybutynin.

Buschmann '737 teach 1-phenyl-3-dimethylaminopropane compounds with an analgesic effect, which are suitable for the treatment of severe pain without giving rise

to the side effects which are typical of opioids, and which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with the opioid tramadol in some cases, and which has a significantly enhanced analgesic effect compared with that of tramadol (col. 1, lines 52-65). Buschmann '737 teaches a method of making and separating the (+) enantiomer of (2R, 3R)- 1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol (Example 1, column 6, line 23 to column 7, line 61). Buschmann '737 teaches that the (+) enantiomer of (2R, 3R)-1-dimethylamino- 3-(3-methylphenyl)-2-methylpentan-3-ol is a superior analgesic compared to the racemic mixture or (-) enantiomer (column 23, Table).

Andersson et al teach pharmaceutical substances that are known to treat urinary incontinence (Title) and include anti-muscarinic (i.e., anticholerinergic) agents such as atropine, propantheline, emepronium, trospium, tolterodine, darifenacin, oxybutynin and propiverine (pages 924 and 925, table 2). Andersson et al teach that one such anti-muscarinic agent, oxybutinin, has well documented efficacy in the treatment of detrusor hyperactivity, is available in various forms, and is probably the drug of first choice in patients with detrusor hyperactivity (page 930, column 2, third and fifth full paragraphs).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to combine an admixture of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation success, for the following reasons: First, one skilled in the art would be motivated to combine an opioid and an anticholinergic agent, since

both are known to impair detrusor contraction, as taught by Chutka et al. It is prima facie obvious to combine two compositions, each of which is taught by the prior art, to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06. Second, one skilled in the art would be motivated to substitute (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride for an opioid, since the aminopropane compound has an enhanced analgesic effect compared to an opioid (and therefore would be reasonably expected to have the same or improved efficacy in relaxing bladder muscles as well) but without the negative side effects, as taught by Buschmann '737. Third, one skilled in the art would be motivated to select oxybutynin as the antimuscarinic agent because oxybutynin is known to be effective as an antimuscarinic agent, and is even known as the "drug of choice", as taught by Andersson et al.

Regarding claim 73, Buschmann '737 teaches that the analgesics are administered with pharmaceutically suitable auxiliary substances (see col. 5, lines 48-67).

Response to Arguments

7. Applicant's arguments filed 8/25/10 have been fully considered but they are not persuasive.

Applicant argues that the compound tested in Example 1 of the specification, (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride, is representative of the presently recited compounds of formula I and the unexpected,

synergistic result for treating urinary incontinence associated with the tested combination is commensurate with the scope of the claims. In response to the Office's position regarding the probative value of the combination of the tested compound and oxybutynin, Applicant argues that Buschmann et al. '737 teaches use of the 1-phenyl-3-dimethylaminopropane compounds as analgesics suitable for the treatment of pain, not for the treatment of urinary incontinence, and thus the test data of Buschmann et al. '737 showing analgesic effect does not support the Office Action's assertion that the unexpected, synergistic effect with regard to treating urinary incontinence associated with the tested combination is not commensurate with the scope of the claims. Applicant also argues that the test results of Example are also commensurate with the scope of the claims even though only one dosage of each compound in the combination was tested. Applicant maintains that synergism is typically not dose dependent, arguing that U.S. Patent 4,442,084 (cited as evidence that synergism is typically dose dependent) does not show dose-dependent synergism.

This argument is not persuasive. Since the mechanism of opioids in treating urinary incontinence is their analgesic effect on the detrusor, impairing contractions of the muscle, as taught by Chutka, one skilled in the art would reasonably expect that the superior analgesic effect of the compounds of Buschmann '737 compared to opioids such as tramodol, as taught by Buschmann '737, would not exclude their analgesic effect on certain muscles, such as the detrusor, and therefore is also indicative of their superior analgesic activity on the detrusor muscle, resulting in superior impairment of detrusor contractions. Therefore, since Buschmann '737 specifically teaches that the

(+) enantiomer of (2R, 3R)-1-dimethylamino- 3-(3-methylphenyl)-2-methylpentan-3-ol exhibits a superior analgesic effect compared to the racemic mixture or (-) enantiomer, the probative value of the combination of the (+) enantiomer and oxybutynin cannot reasonably be extended to other 1-phenyl-3-dimethylaminopropane compounds of formula I in the claimed invention.

Even if the probative value data of the (+) enantiomer could reasonably be extended to other compounds of formula I of the claimed invention, it is noted that only one dose of each compound in the combination is tested in Example 1 of the specification, but the claims are drawn to each compound in any amount. As stated previously, one skilled in the art would reasonably expect synergism to be dose dependent because, if the amount of one of the components is very small, it would not be expected to contribute to the efficacy of the combination. Conversely, if the amount of one of the components is very large, one skilled in the art would not expect the addition of another component to potentiate the effects of the component present in large amounts. Therefore, one skilled in the art would reasonably expect there to be a range of dosages at which synergism might occur. Since Applicant has provided data for only a single dosage of each component in the composition, one of ordinary skill in the art would not be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof to any dosage amount of each compound. See MPEP 716.02(d). Applicant's arguments that U.S. Patent 4,442,084 does not teach dose-dependent synergism are not persuasive because they contradict the direct teachings of the '084 patent, which states, **"a dose dependent**

synergism is evidenced in the above test" (col. 6, lines 40-44). Patent '084 further states that a range of dosages to be tested was first determined prior to testing, based on the ED_{50} valued previously established for the individual components (col. 6, lines 12-15), and that the super-additive synergistic activities for the components A and B were **at the tested ratios**, not at any amount (col. 7, lines 11-15), thereby providing evidence that its synergism is dose dependent.

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Ashwin Mehta/
Primary Examiner, Technology Center 1600